Rôle des protéines matricielles dans l’hypoxie et l’angiogenèse / Role of matrix proteins in hypoxia and angiogenesis

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PUBLICATIONS


CIRCUITS NEURONAUX ET COMPORTEMENT / NEURAL CIRCUITS AND BEHAVIOR

Responsable : Alexander FLEISCHMANN

PUBLICATIONS


RÔLE DES PROTÉINES MATRICIELLES DANS L’HYPOXIE ET L’ANGIOGENÈSE / ROLE OF MATRIX PROTEINS IN HYPOXIA AND ANGIOGENESIS

Responsable : Stéphane GERMAIN

RECHERCHE

The sequence of biological events that permits an organism to maintain tissue viability in hypoxia remains poorly understood. Variations in oxygen concentration lead to respiratory, metabolic and vascular adaptations in tissues. How hypoxic
endothelial cells (EC) integrate chemical signals with mechanical cues from their local tissue microenvironment in order to produce functional capillary networks that exhibit specialized form remains an open question. A key role of hypoxia in the regulation of many endothelial functions is nevertheless well established and growing evidence show that angiogenesis, defined as the events leading to blood vessels formation by sprouting or growth of preexisting vessels, can be triggered by hypoxia, both during development and in pathological conditions, such as cardiovascular ischemia and tumors. Our team is interested in understanding how angiogenesis and vascular integrity are regulated in hypoxic conditions.

We are using a multidisciplinary approach combining gene discovery approach for complex human diseases, vascular cell biology (endothelial and smooth muscle cells) cell cultures in 2-D and 3-D, biochemistry, molecular biology, various imaging approaches (confocal analyses, light sheet microscopy, videomicroscopy), gene expression analyses, protein production, and preclinical models of human diseases.

Dynamic control of endothelial cell junctions is essential for vascular homeostasis and angiogenesis. We provided genetic evidence that ANGPTL4 (angiopoietin-like 4) is a key regulator of vascular integrity both during developmental and in hypoxia-induced pathological conditions. We recently reported that myocardial infarct size is increased in ANGPTL4 KO mice. Intravenous administration of human recombinant ANGPTL4 induces subsequent protection from vascular permeability and finally reduced infarct size and the no-reflow phenomenon. We further showed for the first time that ANGPTL4 serum levels predict MRI-detected no-reflow after successful PCI in STEMI patients.

In stroke, we also showed that ANGPTL4 modulates EC permeability following ischaemia/reperfusion and thus represents a potential new therapeutical target.

Mechanistically, ANGPTL4-αvβ3 interaction enhances Src recruitment to integrin αvβ3 and inhibits Src signalling downstream of vascular endothelial growth factor receptor 2 (VEFGR2), thereby repressing hypoxia-induced breakdown of VEGFR2-VE-cadherin and VEGFR2-αvβ3 complexes. We further demonstrate that intravitreal injection of recombinant human ANGPTL4 limits vascular permeability and leads to increased adherens junction and tight junction integrity. These findings identify a novel mechanism by which ANGPTL4 counteracts hypoxia-driven vascular permeability through integrin αvβ3 binding, modulation of VEGFR2-Src kinase signalling, and endothelial junction stabilization.

Given the recently demonstrated therapeutic role of ANGPTL4 (our 2 patents) in diminishing no-reflow and therefore infarct size in pre-clinical animal models, these findings in humans may open new fields of research.

By gain-of-function and loss-of-function approaches, both in vitro and in vivo, we are also studying ECM composition, deposition, posttranslational modifications and rearrangement by ECs. Indeed, hypoxia-driven vascular remodeling is dynamically regulated through activities of ECM modifying enzyme, such as Lysysl Oxidase like 2 or Transgluaminase-2 that eventually regulate both matricellular proteins and growth factor availability, that eventually affect angiogenesis.

We investigated the effect of Transgluaminase-2 (TG2), which binds to HSPGs, on the interaction between VEGF165 and HS and angiogenesis. Mice with tg2-deficiency showed transiently enhanced retina vessel formation and increased vascularization. EC in which TG2 was knocked down exhibited enhanced VEGF165-induced sprouting and migration, which was associated with increased phosphorylation of VEGFR2 at Tyr(951) and its targets Src and Akt. These results
show that TG2 controls the formation of VEGF165-HSPG complexes which could be pharmacologically targeted to modulate angiogenesis.

Our team also identified lysyl oxidase the like 2 (LOXL2) as a major target of hypoxia in the EC extracellular matrix. Recent work by the team, showed that LOXL2 has a scaffolding function in the extracellular matrix which affects cell-matrix interactions and subsequently the mechanotransduction of properties involved in the morphogenesis of capillaries. Manuscript in preparation.

We identified fibroblast growth factor-2 (FGF-2) as a potent inducer of the release of VEGF and hepatocyte growth factor (HGF) by dental pulp stem cells derived from deciduous teeth (SHED). Using 3D culture models of angiogenesis, we demonstrated that VEGF and HGF were both responsible for the high angiogenic potential of SHED. We then applied in vitro FGF-2 priming to SHED before encapsulation in hydrogels and in vivo subcutaneous implantation thereby demonstrating that FGF-2 priming enhances the angiogenic potential of SHED.

Altogether, our studies aimed at better understanding of the complex interplay between ECs and soluble growth factors and mechanical factors from the ECM will certainly have significant implications for understanding the regulation of developmental and pathological angiogenesis driven by hypoxia.

**Publications**


**Chevalier N.R., Gazquez E., Bidault L., Guibert T., Vias C., Vian E., Watanabe Y., Muller L., Germain S., Bondurand N., Dufour S. et Fleury V., « How tissue mechanical properties affect enteric neural crest cell migration », Scientific Reports, vol. 6, 2016, p. 20927, DOI: 10.1038/srep20927.**


ÉQUIPES ACCUEILLIES AU COLLÈGE DE FRANCE


COMMUNICATION JONCTIONNELLE ET INTERACTION ENTRE GLIAL ET NEURONE / *JUNCTIONAL COMMUNICATION AND INTERACTIONS BETWEEN GLIAL AND NEURONAL NETWORKS*

Responsable : Christian GIAUME

**PUBLICATIONS**


LIU X., GANGOSO E., YI C., JEANSON T., KANDELMAN S., MANTZ J. et GIAUME C., « General anesthetics have differential inhibitory effects on gap junction channels and hemichannels in astrocytes and neurons », *Glia*, vol. 64, n° 4, 2016, p. 524-536, DOI : 10.1002/glia.22946.


